PEDIATRIC SCIENCES JOURNAL
The Official Journal of the Pediatric Department, Faculty of Medicine, Cairo University, Egypt

Original Article

Acute Kidney Injury In Children Admitted In Pediatric Intensive Care Unit

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Received: 22/3/2022; Accepted: 26/5/2022; Published online: 1/7/2022

Abstract:
Background: Acute kidney injury (AKI) poses a significant burden for the society, in terms of health resource use during the acute phase, and the potential long-term sequelae including development of chronic kidney disease and kidney failure.
Aim of the work: to investigate the risk of development of AKI in critically ill children.
Material and methods: A cohort study conducted on 60 critically ill children admitted at pediatric intensive care unit (PICU). They were divided into two groups according to hemodynamic stability. Cardiovascular parameters together with criteria for AKI were observed during the first 5 days of PICU admission. AKI was diagnosed based on Acute Kidney Injury Network criteria.
Results: From all critically ill included patients (60 patients); thirty four patients developed AKI (56.6%). Frequency of AKI was significantly more in hemodynamically unstable than stable patients 22 (73%) versus 12 (40%) (p=0.018). AKI was strongly associated with decreased baseline systolic and diastolic blood pressure percentiles (p=0.04) and (p=0.049), increased doses and duration of inotropic support determined by vasoactive inotropic score (p=0.002) and (p=0.013) respectively, higher base deficit in baseline blood gases (p=0.002), multiple organ dysfunctions (p<0.001) and exposure to nephrotoxic agents (p=0.036).
Conclusion: AKI is a common morbidity among hemodynamically unstable critically ill children. AKI is strongly associated with initial hypotension on admission, increased doses and longer duration of inotropic support, increased base deficit in initial blood gases evaluation, multiple organ dysfunctions and exposure to nephrotoxic agents.

Level of Evidence of Study: IIA. (*1*)
Keywords: Acute kidney injury; hemodynamic instability; pediatric intensive care unit.
Abbreviations: AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BP: blood pressure; BUN: blood urea nitrogen; CI: cardiac index; CNS: central nervous system; CVP: central venous pressure; DBP: diastolic arterial blood pressure; ICU: intensive care unit; INR: International normalized ratio; IQR: inter-quartile range; MAP: mean arterial blood pressure; MV: mechanical ventilation; PC: prothrombin concentration; PICU: pediatric intensive care unit; PT: prothrombin time; ROC: receiver operating characteristic RRT: renal replacement therapy; SBP: systolic arterial pressure; ScvO2: central venous oxygenation saturation; SD: standard deviation; SV: stroke volume; SVR: systemic vascular resistance; SVRI: systemic vascular resistive index; SVV: stroke volume variability; TFC: thoracic fluid content; UOP: urine output; VIS: vasoactive inotropic score.

Introduction

Acute kidney injury (AKI) is a common complication in patients admitted to the intensive care unit (ICU) and is associated with adverse outcomes including increased length of ICU and hospital stay and increased short and long-term mortality risk (*2*). Despite harmonization in clinical definition and staging, identification of novel renal biomarkers for clinical use, and progress in understanding the underlying pathophysiology of AKI; it remains a major unmet

medical need without effective pharmacological treatments. It continues to be a global public health concern impacting about 13.3 million patients per year (*3*).

It was demonstrated that the most frequent causes of AKI in the critically ill patients are sepsis and hypovolemia followed by nephrotoxic agents (*4*). However, the cause of AKI is often multifactorial with pre-existing comorbidities further increasing the risk (*5*). The renal microvasculature plays a key role in the pathophysiology of AKI. The kidney has a high energy demand with a relatively low net oxygen extraction, yet the oxygenation of the outer medulla is quite marginal and the vascular architecture in this region is very susceptible to further compromise of vascular perfusion and oxygenation (*6*). In recent years, new technologies have come to determine hemodynamic indices. These new technologies are highly diverse, ranging from very invasive to less invasive or even noninvasive, from intermittent to continuous, and involving different basic principles, methods and costs. Some of the methods offer dynamic fluid response indices, which are currently regarded as better predictors of the response to volume expansion, while others allow us to evaluate volumetric preload parameters or afford continuous central venous saturation measurements. All of these variables, together with cardiac output, contribute to improve the hemodynamic monitoring of critical ill patient (*7*). The current cohort study aimed to investigate the association between systemic hemodynamic indices and the risk of development of AKI or its contributing risk factors in critically ill children.

Subjects and Methods

This cohort study was conducted on 60 critically ill children with or without cardiovascular compromise who were admitted at PICU, Cairo University Children Hospital. They were observed for 5 days from PICU admission. The study had been approved by the Research Ethics Committee, Faculty of Medicine, Cairo University, and that had been conducted in accordance with the principles set forth in the Helsinki Declaration (*8*).

Participants

The calculated sample size was 60 patients using the following formula: $\frac{n= 2\ \sigma 2\ (Z\ a/2 + Z\ b)}{d2}$

Where:

n = sample size,

Z a/2 = the critical value of the Normal distribution at α/2, (1.96);

Z b= the critical value of the Normal distribution at β,(1.282);

σ = population standard deviation, d = true mean difference.

Inclusion criteria in the study: children aged 1month–16 years and of both sexes critically ill children need PICU admission and monitoring with or without hemodynamic instability. Hemodynamic instability was defined as: hypotension or reduced tissue perfusion (capillary refill>2 sec) despite adequate fluid resuscitation and in need for significant inotropes /vasopressor support (>100mic /kg/min) of any inopressors (*9*). Exclusion criteria: patients known to have chronic renal failure or end stage renal disease on renal replacement therapy, patients with AKI due to intrinsic renal failure as rapidly progressive glomerulonephritis, hemolytic uremic syndrome……etc, patients with AKI due to post renal failure as renal stones, stricture, posterior ureteral valve……etc. After explaining the purpose of the study to the parents and taking informed consents from them for participation in the research study, all included patients were subjected to the following: History taking and clinical assessment; that included age, sex, body weight that was measured in kilograms. It was plotted on Egyptian growth curves (*10*) and the patient was considered underweight if the percentile was below 3rd percentile (*11*). Also, data about co-morbidities, chronic illnesses, system(s) failure and system(s) support (respiratory or cardiovascular failure), or multi-organ system failure were collected.

Methods

Multi-organ dysfunction was defined as failure of three organs or more excluding the kidney (*12*), according to pediatric organ dysfunction criteria (*13*):

Cardiovascular dysfunction:

Despite administration of isotonic intravenous fluid bolus ≥ 40 ml/kg in 1 hour:

- Decrease in BP (hypotension) < 5th percentile for age or systolic BP > 2 SD below normal for age OR
- Unexplained metabolic acidosis: base deficit > 5.0 mEq/L
- Increased arterial lactate > 2 times upper limits of normal
- Oliguria: urine output < 0.5 mL/kg/hr.
- Prolonged capillary refill: > 5 secs
- Core to peripheral temperature gap > 3°C.

Respiratory dysfunction:

- PaO2/FiO2 < 300 in absence of cyanotic heart disease or preexisting lung disease OR
- PaCO2 > 65 mmHg or 20 mmHg over baseline PaCO2 OR
- Proven need for > 0.50 FiO2 to maintain SaO2 ≥ 92% OR
- Need for non-elective invasive or noninvasive mechanical ventilation

Hematologic dysfunction:

- Platelet count < 80,000/mm3 or a decline of 50% in platelet count form highest value recorded over the past 3 days (for chronic hematology/oncology patients) OR
- International normalized ratio (INR) > 2

Hepatic dysfunction:

- Total bilirubin ≥ 4 mg/dL (not applicable to the newborn) OR
- ALT twice the upper limit of normal for age.

Vasoactive inotropic score

Patients on inotropic support were evaluated by vasoactive inotropic score (VIS). VIS= dopamine dose (μg/kg/min) +dobutamine dose (μg/kg/min) +100× epinephrine dose (μg/kg/min) +100×norepinephrin dose (μg/kg/min) + 10×milrinone dose(μg/kg/min)+10000×vasopressin dose (U/kg/min). VIS was calculated as a weighted sum of all administered inotropes and vasoconstrictors, reflecting pharmacological support of the cardiovascular system (*14*). Limited studies explored the VIS cutoff (> 20) (*15*). The threshold of vasoactive–inotropic score (> 42.5) was independently associated with PICU mortality (*16*).

Hemodynamic parameters assessment

The following hemodynamic parameters were evaluated during the first 24 hours after PICU admission:

- Central venous pressure (CVP)
- Systolic arterial pressure (SBP)
- Diastolic arterial blood pressure (DBP)
- Readings were plotted on Egyptian nomograms for establishment of blood pressure in Egyptian children (*17*) and on PICU chart in PICU handbook of University of lowa Stead Family Children Hospital for normal values SBP and DBP according to age (*18*). The patients were divided into normo-tensive (BP percentiles were between 50th and 95th percentiles and normal for age and sex), hypotensive (BP percentiles were below 50th percentile and low for age and sex) and hypertensive (BP percentiles was above 95th percentile and high for age and sex) patients.
- Mean arterial blood pressure (MAP)
- Because of hemodynamic variations during the unstable initial phase, the lower limits and the upper limits of the range (ULR) and the mean value of blood pressure over the first 24 hours was recorded.
- Central venous oxygenation saturation (ScvO2): sample was taken after fluid resuscitation and insertion of central venous line.
- Impedance Cardiometry readings were recorded before and after inotropic and vasopressor support. Electrical cardiometry (ICON; Cardiotronic/Osypka Medical Inc., La Jolla, California, USA) is one of the recent and noninvasive technologies. It estimates cardiac parameters by measuring changes in thoracic electrical bioimpedance during the cardiac cycle. The electric cardiometry, using four electrocardiogram electrodes, estimates the maximum rate of change of impedance to peak aortic blood acceleration based on the principle that red blood cells change from random orientation during diastole (high impedance) to an aligned state during systole (low impedance). This device estimates cardiac index (CI), stroke volume (SV), systemic vascular resistance (SVR), and a variety of other cardiac parameters (*19*).

Daily fluid balance

- It was calculated as the fluid input (volume of colloids, crystalloids and feeding) minus fluid output (urine output, fluid from drains, gastric aspiration and insensible water losses).

Clinico-laboratory data

- It was recorded to diagnose development or persistent AKI in both groups of critically ill patients (both hemodynamic instable and stable) which including: baseline and follow up serum creatinine, blood urea nitrogen (BUN), accurate estimation of urine output (UOP) and its correction to body weight /surface area, and the need for renal replacement therapy (RRT).
- Also, complete blood count, blood gases, and liver function tests were recorded.

Diagnosis of AKI

- It was based on the Acute Kidney Injury Network (AKIN) classification:
- Increase in serum creatinine level >50% from baseline or ≥0.3 mg/dl or oliguria (UOP <0.5 ml/kg/h for 6 hours) (*20*).
- New AKI is defined as an increase in serum creatinine level 0.3 mg/dl or >50% compared to baseline value or need for RRT after the first 24 hours from admission in patients who had no AKI upon admission.
- Persistent AKI is defined as a steady or increase in AKIN classification stage between the first 24 hours following admission and day 5 in patients with AKIN stage ≥1 at the time of inclusion in the study (*21*).
- The outcome of all included cases till being discharged from PICU was reported. The endpoint of the study was the development of a new AKI or persistent AKI during the 5 days following ICU admission.
- In order to extract risk factors/ predictors of AKI development in critically ill children; all included patients were divided into: no AKI group and AKI group. Both groups were compared as regard different demographic, clinical, hemodynamic, laboratory parameters and exposure to nephrotoxic medications.

Statistical analysis

Data were analyzed using NCSS© 12 Statistical Software 2018 (NCSS, LLC. Kaysville, Utah, USA). Skewed numerical data were presented as median and interquartile range and intergroup differences were compared using the Mann-Whitney U test. Descriptive data was expressed using mean and standard deviation. Categorical data were presented as number and percentage and intergroup differences were compared using Fisher's exact test. Ordinal data were compared using the chi-squared test for trend evaluation. The diagnostic value of clinical, biochemical or echocardiographic measures was examined using receiver-operating characteristic (ROC) curve analysis. P-values <0.05 were considered statistically significant.

Results

The current cohort study included 60 critically ill children admitted at PICU, Cairo University Children Hospitals. Included patients were divided into 2 groups based on their hemodynamic assessment during the first 24 hours of PICU admission: group (A): hemodynamically stable patients (30 patients) and group (B): hemodynamically unstable patients (30 patients). The mean age ± SD of group A is 30.8 ± 35.5 months (range from 3-144 months and that of group B was 22.6 ± 29.5 months (range from 2-120 months) (p=0.3).The high standard deviation indicates greater variability in data points, or higher dispersion from the mean.

Demographic data

In group (A); 50% of patients were males, while in group (B), males represented about 46.7% of patients with no significant difference between both groups (p = 0.9). The median age of included patients was 19 months with inter-quartile range (IQR) from 8 to 36 months in group A, while it was 11 months with IQR from 5 to 24 months in group B with no statistically significant difference between group A and group B (p = 0.337). All included patients had normal body weight for age and sex except 5 patients in group B and 3 patients in group A who were underweight (their weight percentile was below third percentile for age and sex according to

Egyptian growth charts (*10*) with no statistically significant difference between the 2 groups (P = 0.34). There was no statistically significant difference between the two groups as regard age or gender of patients (p=0.3) and (p=0.9) respectively.

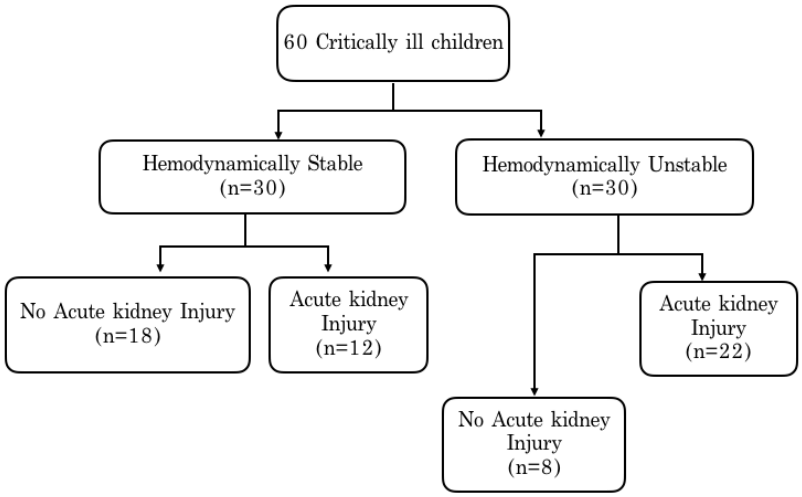

Figure 1. Flowchart of Studied Children.

Table 1: Number of systems affection in the study groups

		Hemodynamically stable group (n=30)		Hemodynamically unstable group (n=30)		P value
		Number	%	Number	%	
Number of dysfunctional systems*	Nil	6	20.0	0	0.0	0.915
	One system	8	26.7	18	60.0	
	Two systems	8	26.7	3	10.0	
	Three systems	5	16.7	8	26.7	
	Four systems	2	6.7	1	3.3	
	Five systems	1	3.3	0	0.0	

***** Respiratory failure, cardiovascular failure, neurologic, hematologic and/ or liver cell failure.

Indication of ICU admission / underlying cause of system failure

The main indication of PICU admission was organ failure (one or more). (Table 1). The affected systems were (according to pediatric Organ Dysfunction Criteria):

Respiratory failure: 41 (68.3%) patients of the study groups were mechanically ventilated (28.3% patients of group A and 40% patients of group B). The duration of mechanical ventilation was significantly longer in group B than group A (difference 2.7 days, p=0.036). This was secondary to chest infection or disturbed consciousness level.

Cardiovascular failure: all patients in group B needed inotropic support. This was secondary to heart failure or septic shock.

Neurologic: Glasgow Coma Score (GCS) ≤ 11 (12 patients in group A and 11 patients in group B). This was secondary to CNS infection and septic shock.

Hematologic: Platelet count < 80,000/mm3 (3 patients in group A and 8 patients in group B). This was secondary to sepsis.

Hepatic: Total bilirubin ≥ 4 mg/dL (one patient in group A and 2 patients in group B). ALT twice the upper limit of normal for age (5 patients in group A and 15 patients in group B). This was secondary to sepsis.

Hemodynamic indices and impedance Cardiometry parameters

Initial systolic and diastolic blood pressure percentiles on PICU admission were significantly higher in the hemodynamically stable group (p<0.001) and (p=0.002) respectively, but no significant difference was found between both groups as regard average percentiles (systolic, diastolic or mean pressures) over the first 24 hours of PICU admission (p=0.86), (p=0.27) and (p=0.67) respectively. (Table 2). The patients were divided according to their initial SBP and

DBP percentiles into normo-tensive, hypotensive and hypertensive groups. Most of the patients in group A had normal (18 patients 60%) initial systolic and diastolic blood pressure percentiles according to their age. 6 patients (20%) were hypertensive and 6 patients (20%) were hypotensive. While all patients in group B had low initial systolic and diastolic blood pressure percentiles according to their age except 3 of them (10%) had normal initial BP percentiles.

According to the presence of AKI, the patients in each group were subdivided into AKI group and no AKI group. (Figure 1). AKI group included 25 patients (73.5%) with hypotension, 3 patients (9%) with hypertension and 6 patients (17.5%) had normal blood pressure. Non AKI group included 8 patients (30.7%) with hypotension, 3 patients (11.5%) with hypertension and rest of the patients (57.8%) had normal blood pressure. Figure 2 shows the blood pressure of the study groups according to percentiles according to Egyptian nomograms for establishment of blood pressure in Egyptian children (*17*).

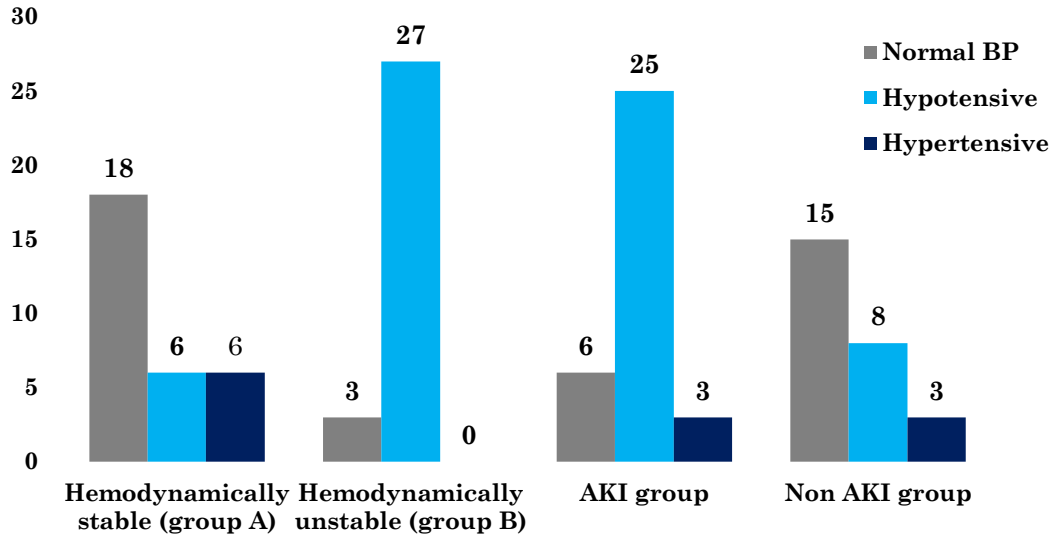

Figure 2. Normal blood pressure, hypertension and hypotension in the study groups.

Table 2. Hemodynamic indices of the 2 study groups.

	Hemodynamically stable (group A)		Hemodynamically unstable (group B)		P value
	Median (IQR)	Mean ±SD	Median (IQR)	Mean ±SD	
Baseline SBP percentiles		66.4 ± 21.9		46.8 ± 8.11	0.0001
Baseline DBP percentiles		66.9 ±11.65		53.1 ±28.6	0.002
Average SBP (mmHg)	108 (96- 115)	105.5 ± 11.2	104.0 (96- 116)	104.3 ± 11.2	0.859
Average DBP (mmHg)	67.5 (65- 76)	69.5 ± 9.8	67.0 (60-73)	66.5 ± 9.5	0.217
Maximum MAP(mmHg)	89 (83- 93)	88.7 ± 11.3	92.5 (85- 100)	93.2 ± 10.3	0.145
Minimum MAP(mmHg)	65.5 (62- 76)	68.3 ± 10.5	65.0 (59- 69)	64 ± 10	0.222
Average MAP(mmHg)	80.2 (73- 84)	79.1±8.9	78.2 (76- 85.5)	69.6±7.4	0.673
SV (ml)	19.4 (14- 29.0)	23.9± 13.5	15.5 (12- 24)	23.6± 24.6	0.119
CI (L/min/m²)	4.6 (3.9-5.6)	4.8 ± 1.5	3.9 (2.8 - 5.1)	4.3 ± 1.8	0.027
Contractility Index	91.5 (69- 117.6)	104 ± 41.4	71.2 (58- 98.2)	125.6 ± 186	0.014
SVV (%)	12.0 (9- 17)	12.9± 4.4	18.0 (10-22.0)	15.6± 5.4	0.018
SVRI	1910 (18- 2599)	1815. 4± 896	1000.0 (890- 1360)	1895. 9± 801.9	0.001
TFC (1/kΩ)	34 (25- 45.0)	35.5 ± 12	40.0 (29- 53)	38.8 ± 23	0.062
Fluid balance on day 1 (ml/kg)	13.3 (8.5-25.3)	18.4 ± 22.3	50.8(16.2-110.5)	61.1 ± 60.9	0.001
Fluid balance on day 5 (ml/kg)	13.4 (8.6-22)	16.3± 12.5	39.2 (22.6-54.1)	36.1± 25.3	0.001
UOP on day 1 (ml/kg)	2.4 (1.6 to 3.1)	2.4 ± 0.99	2.8 (1.6 to 4.2)	3.1 ± 2.2	0.211
UOP on day 5 (ml/kg)	2.8 (2.0 to 3.7)	2.8 ±1	2.8 (1.9 to 3.8)	3 ± 1.9	0.63

CI: cardiac index; CVP: central venous pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure; SVRI: systemic vascular resistive index; SVV: stroke volume variability; TFC: thoracic fluid content; UOP: urine output.

The average mean CVP readings over first 24 hours of PICU admission of groups A and B were 7.7(±2.5) and 7.1 (±2.9) with no significant difference between both groups (p=0.469). Before inotropic support; CI, contractility index and systemic vascular resistive index (SVRI) readings

were significantly lower, while stroke volume variability (SVV) was significantly higher in hemodynamically unstable group than stable patients (p=0.027), (p=0.014), (p=0.001) and (p=0.18) respectively. Fluid balance was calculated at the end of first 24 hours and at the end of 5 days of PICU admission. Hemodynamically unstable patients had significantly increased positive fluid balance than stable group (p<0.001) in both first day and 5 days of PICU admission. No statistically significant difference was found between group A and group B regarding UOP in first and fifth days of PICU admission.

Mechanical ventilation

Median duration of mechanical ventilation (MV) was 1.5 with IQR from 0 to 5 days in hemodynamically stable group and it was 4 with IQR from 1 to 8 days in hemodynamically unstable group. It was significantly longer in hemodynamically unstable group than hemodynamically stable group (p 0.036).

Laboratory data

Platelets count was significantly lower in hemodynamically unstable group by day 5 of PICU admission than that of stable group (p=0.032). The median base excess initial value at day 1 PICU admission of group B (-11) was significantly higher than that of group A (-4.2) (p<0.0001) reflecting more tissue hypoxia in the hemodynamically unstable group at PICU admission. Blood urea nitrogen (BUN) and serum creatinine on day 1 ICU admission were significantly higher in hemodynamically unstable group than that of stable group (p=0.001) and (p=0.033) respectively. Peak serum creatinine (maximum level reached through 5 days observation) and delta creatinine (difference between highest and lowest value) levels were significantly higher in unstable group. No significant difference between both groups as regard other laboratory parameters. (Table 3).

Table 3. Laboratory data of the study groups.

	Hemodynamically stable (n=30)		Hemodynamically unstable (n=30)		P value
	Mean	SD	Mean	SD	
Hemoglobin on day 1 (g/dl)	9.5	2.3	9.5	1.8	0.980
Hemoglobin on day 5 (g/dl)	10.5	1.8	10.7	1.6	0.596
Platelets on day 1 (k/mm3)	270.8	156.0	228.4	186.9	0.344
Platelets on day 5 (k/mm3)	234.0	126.9	165.0	116.4	0.032
TLC on day 1 (k/mm3)	9.9	6.4	12.7	10.4	0.231
TLC on day 5 (k/mm3)	12.2	8.0	12.3	6.3	0.980
ALT (IU/l)	142.9	508.6	176.7	247.8	0.744
AST (IU/l)	185.7	541.8	377.0	612.1	0.205
Total bilirubin (mg/dl)	1.6	5.0	1.6	2.5	0.951
Direct bilirubin (mg/dl)	0.8	3.6	0.8	1.8	0.973
PT (seconds)	17.1	9.3	28.2	35.5	0.101
PC (%)	75.2	19.1	73.0	17.2	0.646
INR	1.59	1.27	1.89	0.95	0.303
	Median (IQR)		Median (IQR)		P value
BUN on day 1 (mg/dl)	17.5 (12 to 23)		27 (18 to 45)		0.001
Creatinine on day 1 (mg/dl)	0.5 (0.33 to 0.6)		0.6 (0.4 to 1.1)		0.033
Creatinine on day 5 (mg/dl)	0.4 (0.35 to 0.8)		0.5 (0.4 to 0.8)		0.338
Base line Creatinine (mg/dl)	0.3 (0.3 to 0.5)		0.3 (0.3 to 0.5)		0.690
Peak creatinine (mg/dl)	0.6 (0.5 to 0.8)		0.8 (0.6 to 1.3)		0.018
Delta creatinine (mg/dl)	0.2 (0.1 to 0.4)		0.4 (0.24 to 0.9)		0.003
Base excess on day 1 (mmol/l)	-4.2 (-5.9 to 1.0)		-11.0 (-15to -8.5)		0.001
Base excess on day 5 (mmol/l)	-2.9 (-4.3 to 2.5)		0.9 (-4.3 to 3.8)		0.169

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; base line creatinine: creatinine before ICU admission; delta creatinine: difference between highest and lowest value; INR: international normalized ratio; PC: prothrombin concentration; peak creatinine: maximum level reached through 5 days observation; PT: prothrombin time; TLC: total leucocyte count.

Acute kidney injury and patient outcome

The percent of patients affected by AKI in group A (stable group) was significantly less than that in group B (unstable group) (40% versus 73.3% with p=0.018). 7 patients had persistent AKI in group A and only one patient needed dialysis, while 13 had persistent AKI in group B and 3

patients in group B needed dialysis but the difference did not reach statistical significance (p=0.606) and (p=0.612) respectively. (Table 4).

Both length of PICU stay and survival were taken in consideration as a final outcome for all included patients. There was no statistically significant difference for patient survival (p value 0.606) or length of PICU stay (p=0.885) between the study groups. (Table 4).

Table 4. Comparison between the two groups as regard development of AKI, patient survival, mortality and length of PICU stay

		Hemodynamically stable (n=30)		Hemodynamically unstable (n=30)		P value
		Number	%	Number	%	
No AKI (n=26)		18	69.2	8	30.8	**0.018**
AKI (n=34)		12	35.3	22	64.7	
Survival	Died	5	16.6	8	26.6	0.606
	survived	25	83.3	22	73.3	
Length of PICU stay (days)		Mean	SD	Mean	SD	0.885
		9.9	6.7	9.7	5.7	

AKI: acute kidney injury; PICU: Pediatric intensive care unit.

Risk factors for development of AKI

In order to extract risk factors/ predictors of AKI development in critically ill children; all included patients were classified into: no AKI group and AKI group. Both groups were compared as regard different demographic, clinical, hemodynamic, laboratory parameters and exposure to nephrotoxic medications.

Hemodynamic indices

Percent of patients developed AKI was significantly higher in hemodynamically unstable patients (p=0.018). (Table 4). Both initial systolic and diastolic blood pressure percentiles at ICU admission were significantly lower in AKI group than non AKI group (p=0.04) and (p=0.049) respectively. Average blood pressure reading within the first 24 hours of ICU admission was not significantly different between both groups. (Table 5). Central venous oxygen saturation was significantly higher in AKI group than no AKI group (p value=0.032). Average CVP was not significantly different statistically between both groups. There was no statistically significant difference between both group as regard fluid balance in day 1 and cumulative 5 day balance.

Table 5. Comparison between the AKI and no AKI groups as regard hemodynamic indices.

	No AKI (n=26)		AKI (n=34)		P value
	Median (IQR)	Mean+/- SD	Median (IQR)	Mean+/- SD	
Baseline SBP percentiles		61.5 +/- 20.6		52.9 +/- 17.2	0.04
Baseline DBP percentiles		66.2 +/-25.1		58.7 +/-30.9	0.049
Average SBP (mmHg)	99 (95-115)	105.5 +/- 11.2	105 (96- 114)	106.3 +/- 12.1	0.416
Average DBP (mmHg)	67.5 (63- 73)	69.5 +/- 9.8	67.5 (60.9- 76)	67.8 +/- 10.7	0.982
Maximum MAP(mmHg)	89.5 (84- 95)	88.7 +/- 11.3	91 (83- 100)	91.2 +/- 12.3	0.676
Minimum MAP(mmHg)	63 (59- 70)	68.3 +/- 10.5	67 (61- 76)	67.2 +/- 11.3	0.387
Average MAP(mmHg)	80.5 (74- 85)	79.5+/-8.3	78 (73- 85)	79.3 +/- 8.1	0.556
ScvO2 on day 1 (%)	68 (64- 78)	69.3 +/- 8.9	76 (68- 82)	74.1 +/- 8.6	0.032
Average CVP(mmHg)	7.3 (6.3- 8)	7.2 +/- 1.9	6.9 (5.5- 9.5)	7.5 +/- 3.1	0.917
Fluid balance on day 1 (ml/kg)	13.8 (9.2- 62.5)	18.4 +/- 22.3	30.1 (14- 77)	43.8 +/- 53.9	0.177
Fluid balance on day 5 (ml/kg)	14.6 (8.6 – 36)	16.3+/- 12.5	25.4 (15.8- 42.9)	28.7+/- 23.4	0.154
UOP on day 1 (ml/kg/hr)	2.4 (1.6- 3.1)	2.4 +/- 0.99	2.9 (1.6 -3.3)	2.8 +/- 2	0.601
UOP on day 5 (ml/kg/hr)	3.1 (1.9- 4.1)	2.8 +/-1	2.8 (1.9 -3.4)	2.8 +/-1.6	0.289
VIS score	0.0 (0.0- 15)	7.7 +/- 14	25.0 (0.0- 30)	23.3 +/- 22.7	0.002
Inotropic support duration (days)	0.0 (0.0 -1)	1 +/- 1.8	2.0 (0.0- 4)	2.2 +/- 2.4	0.013

ScvO2: central venous oxygen saturation; CVP: central venous pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure; SVRI: systemic vascular resistive index; SVV: stroke volume variability; TFC: thoracic fluid content; UOP: urine output

No statistically significant difference was found between no AKI group and AKI group regarding UOP in both first and fifth day of PICU admission. Incidence of AKI was higher with increased both numbers and duration of inotropic supports (p=0.002) and (p=0.013) respectively. (Table 5).

Impedance Cardiometry parameters

Thoracic fluid content (TFC) and SVV showed statistically significant difference between non AKI and AKI group before inotropic support with p value of 0.033 and 0.026 respectively. (Table 6). There was no statistically significant difference between no AKI and AKI group as regard Cardiometry parameters after inotropic support. (Table 6).

Table 6. Cardiometry parameters before and after inotropic support in both groups

	No AKI (n=26)		AKI (n=34)		P value
	Before inotropic support				
	Median (IQR)	Mean ±SD	Median (IQR)	Mean ±SD	
SV (ml)	15.2 (11.6- 29)	23.9± 13.5	18.2 (13.4- 29)	24.5± 16.2	0.233
CI (L/min/m²)	4.2 (3.6- 5.4)	4.8 ± 1.5	4.4 (3.1- 5.5)	4.4 ± 1.7	0.935
Contractility index	81.5 (65- 103)	104 ± 41.4	93 (59- 114)	93.8 ± 39.2	0.596
SVV (%)	12 (9- 16)	12.9± 4.4	18 (10- 22)	16.8± 6.9	**0.026**
SVRI	1696 (940- 2599)	1815. 4± 896	1127 (922- 1413)	1274. 4± 509.3	0.110
TFC (1/kΩ)	33 (25- 42)	35.5 ± 12	40.5 (33- 52)	41.9 ± 13.9	**0.033**
	After inotropic support				
SV (ml)	16 (12.5 – 23)	29.4±37.8	16.3 (12.8 -23)	20.7±12.4	0.796
CI (ml/kg/min)	4.2 (3.3- 6.35)	4.5 ±2	4.3 (2.9- 5.1)	4.2±1.7	0.778
TFC (1/kΩ)	38 (31- 43.5)	38±9.1	32.5 (28- 42)	39.1±26.5	0.372
Contractility index	88.5 (56.8- 122.6)	88.8± 37.6	95.6 (68.9 – 109)	138.9±215.8	0.725
SVV (%)	17 (10- 19.5)	15.5 ± 5.6	18 (12- 20)	15.7±5.4	0.833
SVRI	1477 (1380- 1595.5)	1621±704.7	1814.5 (1342- 2452)	1995±826.6	0.174

AKI: acute kidney injury; CI :cardiac index; SV: stork volume; SVRI: systemic vascular resistive index; SVV: stroke volume variability; TFC (thoracic fluid content).

Table 7. Laboratory parameters of the study groups.

	No AKI (n=26)		AKI (n=34)		P value
	Mean	SD	Mean	SD	
Hemoglobin on day 1 (g/dl)	9.7	2.1	9.4	2.0	0.636
Hemoglobin on day 5 (g/dl)	10.5	1.9	10.6	1.5	0.774
Platelets on day 1 (k/mm3)	280.8	189.3	225.8	156.1	0.222
Platelets on day 5 (k/mm3)	226.2	126.9	179.1	122.6	0.151
TLC on day 1 (k/mm3)	10.6	6.2	11.8	10.3	0.599
TLC on day 5 (k/mm3)	12.2	8.0	12.3	6.3	0.980
ALT (IU/l)	113.7	222.2	195.1	491.3	0.436
AST (IU/l)	259.7	611.7	297.9	565.5	0.803
Total bilirubin (mg/dl)	0.8	0.5	2.2	5.2	0.163
Direct bilirubin (mg/dl)	0.2	0.2	1.3	3.7	0.148
PT (s)	26.3	38.9	19.9	8.6	0.353
CRP (mg/l)	31.5	50.2	33.5	36.6	0.857
BUN (mg/dl)	21.2	10.9	32.7	23.0	**0.022**
Creatinine on day I (mg/dl)	0.5	0.1	0.9	0.8	**0.005**
Creatinine on day 5 (mg/dl)	0.5	0.2	0.9	0.9	**0.012**
Base line creatinine (mg/dl)	0.4	0.1	0.4	0.2	**0.831**
Peak creatinine (mg/dl)	0.5	0.2	1.3	0.9	**<0.001**
Delta creatinine (mg/dl)	0.1	0.1	0.9	0.8	**<0.0001**
Base excess D 1 (mmol/l)	-5.1	4.7	-9.9	6.4	**0.002**
Base excess D 5 (mmol/l)	0.0	3.8	-2.3	6.8	0.137

AKI: acute kidney injury; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; base line creatinine: creatinine before ICU admission; delta creatinine: difference between highest and lowest value; INR: international normalized ratio; PC: prothrombin concentration; peak creatinine: maximum level reached through 5 days observation; PT: prothrombin time; TLC: total leucocyte count.

Mechanical ventilation

Fifteen and 26 patients of non AKI group and AKI group needed MV respectively. As regard duration of MV; AKI group showed an increase of duration on MV, with no statistically significant difference between both groups.

Laboratory data

As anticipated, all kidney function test parameters were significantly elevated in AKI group than no AKI group except initial creatinine at admission. AKI group showed a decreased in base excess values than no AKI group (p value =0.002) in day 1 while in day 5 there was no statistically significant difference between both groups (p value = 0.134). No significant difference between AKI group and no AKI group as regard other laboratory parameters. (Table 7).

Multi-organ system affection

It was significantly related to the development of AKI with increased number of system affection (p<0.001). (Table 8).

Nephrotoxic medications

Significant correlation was found between exposure to nephrotoxic medications and development of AKI (p=0.036). Development of AKI also significantly correlated with duration of exposure (p=0.008). (Table 8).

Patient outcome

Development of AKI was not associated with patient LOS or patient mortality. (Table 8).

Diagnostic value of Receiver-operating characteristic (ROC) curve analysis

Systolic blood pressure

The statistically significant area under the curve is 0.745, with 95% confidence interval of (0.616- 0.849). At a cut off value of (≤76) SBP on admission can predict occurrence of AKI with sensitivity of 62% and specificity of 88%. (Figure 3 and Table 9).

Diastolic blood pressure

The statistically significant area under the curve is 0.753, with 95% confidence interval of (0.625- 0.856). At a cut off value of (≤54) DBP on admission can predict occurrence of AKI with sensitivity of 74% and specificity of 88%. (Figure 3). (Table 9).

Table (8): Comparison between AKI and no AKI groups as exposure to nephrotoxic drugs

		No AKI (n=26)		AKI (n=34)		P value
		Number	%	Number	%	
Number of dysfunctioning systems	0	6	23.1%	0	0.0%	<0.001
	1	14	53.8%	12	35.3%	
	2	4	15.4%	7	20.6%	
	3	2	7.7%	11	32.4%	
	>3	0	0.0%	4	11.7%	
Exposure to nephrotoxins	NO	16	61.5%	11	32.4%	0.036
	YES	10	38.5%	23	67.6%	
Survival	Died	4	15.3%	9	26.4%	0.07
	Survived	22	84.6%	25	73.5%	
Duration of exposure (days)		Mean	SD	Mean	SD	
		2.1	3.7	5.4	5.1	**0.008**
ICU LOS (days)		10.3	7.4	9.4	5.1	0.594

AKI: acute kidney injury; PICU: Pediatric intensive care unit.
Nephrotoxins included aminoglycoside, vancomycin and ACE inhibitors (angiotensin converting enzyme)

Inotropic support score (VIS score) and duration

The statistically significant area under the curve is 0.716, with 95% confidence interval of (0.58- 0.83). At a cut off value of (>21.5) VIS score can predict occurrence of AKI with sensitivity of 59% and specificity of 81%. (Figure 3). (Table 9).

Base excess

The statistically significant area under the curve is 0.733, with 95% confidence interval of (0.603- 0.839). At a cut off value of (≤-5.6) base excess on admission can predict occurrence of AKI with sensitivity of 79% and specificity of 65%. (Figure 3). (Table 9).

Table 9. ROC curve analysis for prediction of new AKI

Predictor	AUC	SE	95% CI	Z	P value	J	Cut-off	Se.	Sp.
SBP (admission)	0.745	0.066	0.616 to 0.849	3.750	0.0001	0.502	≤76	62	88
DBP (admission)	0.753	0.067	0.625 to 0.856	3.768	0.0001	0.620	≤54	74	88
VIS	0.716	0.061	0.585 to 0.825	3.518	0.000	0.396	>21.5	59	81
BE on admission	0.733	0.067	0.603 to 0.839	3.503	0.001	0.448	≤-5.6	79	65

AKI: acute kidney injury; BE: base excess; CI: 95% confidence interval; DBP: diastolic blood pressure; J: Youden J index ([sensitivity + specificity] -1); SBP: systolic blood pressure; Se.: sensitivity; SE: standard error, 95%; Sp.: specificity; ROC: receiver-operating characteristic curve; VIS: vasoactive inotropic Score; Z: Z statistic.

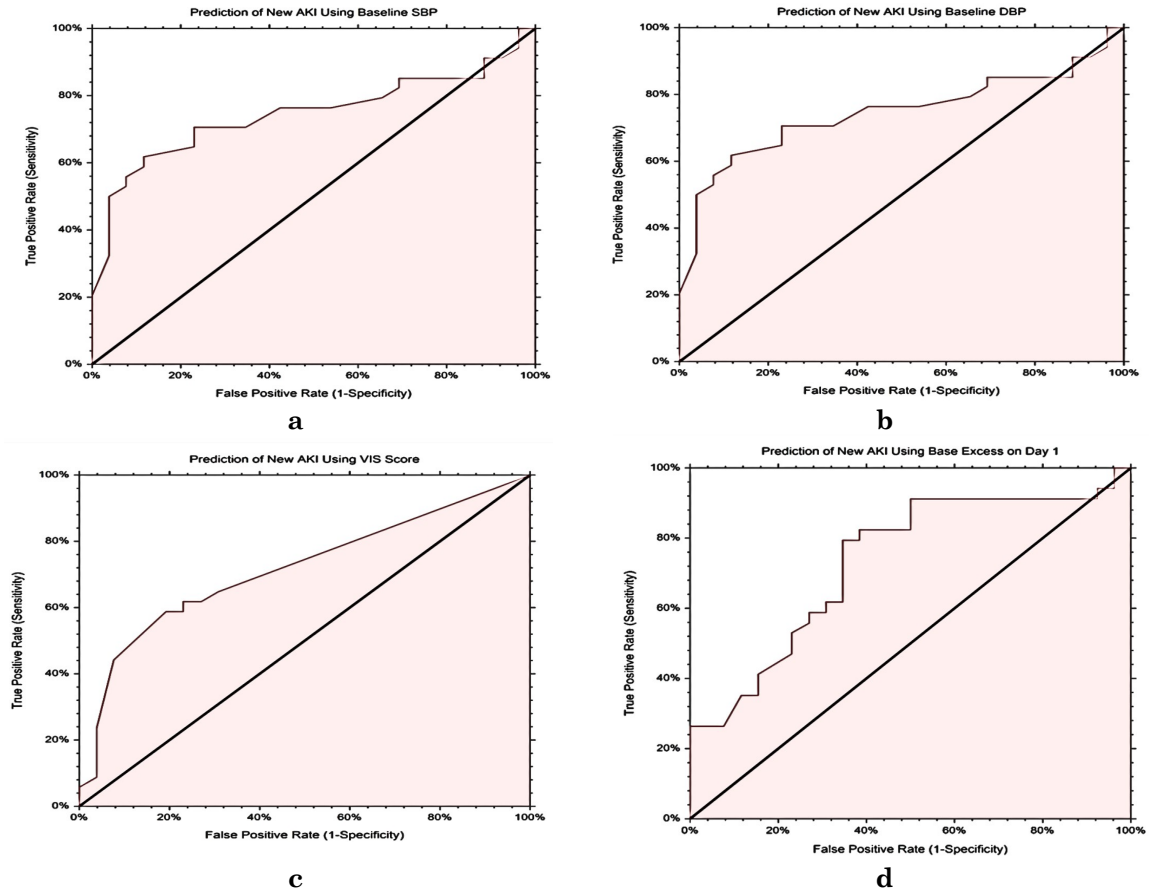

Figure 3. ROC curve Prediction of Acute Kidney Injury (AKI) Among our studied Cohort using (a) baseline systolic blood pressure percentiles; (b) baseline diastolic blood pressure percentiles; (c) Vasoactive inotropic score; (d): base excess on day 1.

Discussion

Critically ill patients often manifest renal insufficiency as part of their disease process. It has become clearer over the past several years that renal failure is independently associated with poor outcome for PICU patients (*22*). AKI imparts significant short and long-term consequences. Despite advances in AKI research, clinical outcomes still unsatisfactory (*23*). Young age, multi-organ system affection, administration of nephrotoxic medications and need of mechanical ventilation are risk factors for AKI. It is associated with longer hospital stay and higher mortality (*24*).

The current cohort study aimed to investigate the association between systemic hemodynamic indices and the risk of development or progression of AKI in 60 critically ill children. Thirty four patients (56%) developed AKI. The percent of patients who developed AKI in the hemodynamically unstable group was significantly higher than that in stable group (73.3% versus 40% with p=0.018). Our rate of AKI among critically ill children is similar to others; who reported AKI in (50.3%) of the patients upon PICU admission based on AKIN criteria (*23*). On the other hand; lower incidence was reported in a large multinational study of the epidemiology of AKI in children and young adults in ICU. They found that AKI occurred in one quarter of patients during the first 7 days after ICU admission (*25*). This variation probably results from differences in case mix, illness severity, coexisting conditions, and definitions of AKI.

Demographic data: in the current study; the development of AKI was not related to age (p=0.51) or male sex in critically ill children who developed AKI (59% versus 35% with p=0.074), contrary to previous reports that male sex and younger age (1month-1 year) were risk factors (*12*, *26*, *27*). The discrepancy between our results and previous reports could be explained by the wide age range of our studied patients.

Hemodynamic indices: In the current study; we found that both SBP and DBP percentiles at PICU admission were significantly lower in AKI group than non AKI group (p=0.04) and (p=0.049) respectively. No significant difference, however, was found between AKI and no AKI patients as regard average SBP, DBP or MBP observed readings over the first 24 hours of PICU admission and after fluid resuscitation. Similarly; a retrospective observational study had identified arterial pressure as not statistically different between the two groups of patients, except for DBP (*23*). Hypotension is a common cause of renal hypoperfusion leading to acute tubular necrosis. The diagnosis is suspected when AKI develops after a hypotensive event, severe sepsis, or drug exposure and is distinguished from prerenal AKI by laboratory testing and response to volume expansion (*28*). Interestingly; it was observed that hypertension in PICU children was associated with AKI (*29*). AKI, however, is a known risk factor for the development of hypertension and chronic kidney disease in children (*30*).

In the current study; CVP was not significantly associated with AKI (p =0.92). Our AKI patients had slightly lower CVP than those with no AKI (6.9 versus 7.3 cm/H_2O). Our finding regard CVP is different from others; who reported that AKI was significantly related to high values of CVP (*23*). This discrepancy could be explained by the fact that all our readings for CVP was obtained after resuscitation as nearly all patient was resuscitated at emergency room before insertion of CVP.

In the current study; we observed increase incidence of AKI with higher dose and longer duration of inotropic support in accordance of previous works. Inotropic support provides enough pressure but not perfusion, hence the renal injury (*30*).

We found that AKI was significantly associated with increased mean ScvO2% during first 24 hour of PICU admission, denoting adequate tissue perfusion and decreased oxygen extraction ratio. In a study done in three participating ICU; the main result of this multi-center observational study was the low incidence of low ScvO2 values (< 70%) in septic patients. Secondary findings were the normal mean ScvO2 values in critically ill patients, including patients with severe sepsis or septic shock. It is also evident in this study that patients show unexpected diverse relation between Scvo2 ratio and incidence of newly onset AKI (*31*).

On the other hand, the role of ischemic hypoxia in AKI is has been proposed in other studies (*32*). Our ScvO2% was the average reading of day 1 of PICU admission. The difference between our finding and others could be explained by the markedly increased fluid resuscitation for our AKI patients to compensate for their initial hypovolemic state on PICU admission (balance was 30 ml/kg versus 13 ml/kg in non AKI patients). ROC curves analysis showed that SVV is a more accurate indicator of fluid responsiveness than CVP in patients with acute circulatory failure (*33*). In our study SVV was significantly more in AKI group (p 0.026) denoting the need of volume expansion during first 24 hour of PICU admission in this group.

Multi-organ system affection: In the current study; we found that multi-organ system affection was significantly related to the development of AKI (p<0.0001). Our finding is supported by similar data by others (*12*). Although the role of renal hypoperfusion is believed to contribute to the development of renal dysfunction, AKI appears to be only partially reversible after optimization of systemic hemodynamics (*34*).

Nephrotoxic medications: Avoidance of nephrotoxic agents is paramount. The list of agents known to be injurious to the kidneys is extensive (*35*). In the present study; AKI was associated with exposure to nephrotoxic agents and with the duration of exposure (p=0.039) and (p=0.008) respectively. In retrospective cohort study conducted by Uber et al (2018); reported that (85.1%) received at least one nephrotoxin; 20.8% received ≥ 3 nephrotoxins. AKI occurred more commonly in those exposed to ≥ 3 nephrotoxins (62.5 vs. 50.8%) (*36*). AKI is often associated with metabolic acidosis, it has become common practice to recommend administration of sodium bicarbonate to correct acid imbalance in AKI patients (*37*). In the current study; AKI is significantly associated with tissue hypoxia manifested by increased base excess in initial blood gases on PICU admission (p=0.002).

The first few hours of PICU admission are the most critical ones. The median onset of AKI was day 1 in hemodynamically unstable patients and day 2 for hemodynamically stable group. This is in concordance with what was recently published that the highest incidence of AKI in ICU patients occurred between day 1 and day 2 of admission, when 28.4% had AKI (*38*).

Patient outcome: In the current study, we found that AKI significantly impact renal outcome (in term of persistent AKI) but insignificantly impacts patient length of PICU stay nor patient mortality. Our findings regard patient outcome does not go with most of the previously reported data of AKI patients (*39*). This could be explained by our short period of patient observation of included patients. The end point of our observation was the development of a new AKI or persistent AKI during the 5 days following PICU admission.

The limitations of our study included that we examined only short term outcomes of hospitalized children with AKI. Also, children with AKI may have long-term residual renal injury e.g., microalbuminuria, hypertension or elevated creatinine levels (*40*). In addition, the study was conducted at a tertiary hospital; the clinical profile of patients could be affected by a referral bias. The current study confirms the significant association between hemodynamic instability within first 24 hours of PICU admission and the development of AKI.

Conclusion

The development of AKI in critically ill children is significantly associated with hemodynamic instability within first 24 hours of PICU admission. AKI is strongly associated with initial hypotension on admission, higher base deficit in initial blood gases evaluation, increased doses and longer duration of inotropic support, multiple organ dysfunctions and exposure to nephrotoxic agents. AKI critically ill patients received more fluid resuscitation and have more ScvO2% and CVP during the first 24 hour observation of PICU admission, denoting adequate response to volume expansion.

Author Contributions: All authors searched medical literature, databases, conceptualized, conducted the case review and reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

FUNDING

Authors declare there was no extramural funding provided for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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